WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Wednesday, April 21, 2004

Hide?	Set Name	Query	Hit Count
	DB=PGPB; PLUR=YES; OP=ADJ		
☐	L1	10/084555	1
	DB=USPT,PGPB,EPAB,DWPI; PLUR=YES; OP=ADJ		
☐	L2	meythyl$ same cancer	0
☐	L3	methyl$ same cancer	3526
☐	L4	methylation same cancer	952
☐	L5	methylation same (proliferat$ near disorder)	98
☐	L6	L4 and regulatory disorder	0
☐	L7	L4 and regulatory region	329
☐	L8	preproenkephalin or ppENK	115
☐	L9	L4 and L8	1
☐	L10	LL7 and L5	0
☐	L11	cpG rich and L4	60
☐	L12	cpG rick and L5	0
☐	L13	hypermethylation and L4	244
☐	L14	hypermethylation and L5	20
☐	L15	L13 and (astrocytoma or glioblastoma or adenoma or leukemia or carcinoma)	209
	DB=PGPB,USPT,EPAB,DWPI; PLUR=YES; OP=ADJ		
☐	L16	L15 and L8	1
☐	L17	pancreatic cancer or colorectal cancer	8870
☐	L18	L17 and L15	107
☐	L19	L18 and hypermethylation	107
☐	L20	L19 and cpG region	0
☐	L21	CpG rich region	72
☐	L22	L21 and L4	41
☐	L23	L22 and L17	13
☐	L24	met5-enkephalin	2
☐	L25	differentially methylated	54
☐	L26	agent or isoschizomer	1447623
☐	L27	L26 and l8	105

☐	L28	L27 and (methyla$ or hypermethylation)	7
☐	L29	(l21 or l22 or l23) and l8	1

END OF SEARCH HISTORY

WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Wednesday, April 21, 2004

Hide?	Set Name	Query	Hit Count
		DB=USPT,DWPI; PLUR=YES; OP=ADJ	
☐	L1	6251594.pn. or 5871917.pn. or 5856094.pn. or 5756668.pn. or 5552277.pn.	10
☐	L2	L1 and (preproenkephalin or ppENK or met5-enkephalin)	0

END OF SEARCH HISTORY

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      (FILE 'HOME' ENTERED AT 15:17:29 ON 21 APR 2004)

      FILE 'STNGUIDE' ENTERED AT 15:17:38 ON 21 APR 2004

      FILE 'HOME' ENTERED AT 15:17:44 ON 21 APR 2004

      FILE 'MEDLINE, BIOTECHDS, EMBASE, BIOSIS, SCISEARCH, CANCERLIT, CAPLUS'
      ENTERED AT 15:20:43 ON 21 APR 2004
L1          1509 S GOGGINS M?/AU OR UEKI T/AU
L2          7576 S PREPROENKEPHALIN OR PPENK OR MET5-ENKEPHALIN
L3        456587 S METHYLA? OR HYPERMETHYLATION OR DIFFERENTIALLY METHYLA?
L4        227492 S PANCREATIC CANCER OR COLORECTAL CANCER OR COLON CANCER
L5          3628 S L4 AND L3
L6            17 S L5 AND L2
L7            10 DUP REM L6 (7 DUPLICATES REMOVED)
L8           123 S L1 AND L3
L9            44 DUP REM L8 (79 DUPLICATES REMOVED)
L10           24 S L9 AND L4
L11           24 DUP REM L10 (0 DUPLICATES REMOVED)

=>
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NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	JAN 27	Source of Registration (SR) information in REGISTRY updated and searchable
NEWS	4	JAN 27	A new search aid, the Company Name Thesaurus, available in CA/CAplus
NEWS	5	FEB 05	German (DE) application and patent publication number format changes
NEWS	6	MAR 03	MEDLINE and LMEDLINE reloaded
NEWS	7	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS	8	MAR 03	FRANCEPAT now available on STN
NEWS	9	MAR 29	Pharmaceutical Substances (PS) now available on STN
NEWS	10	MAR 29	WPIFV now available on STN
NEWS	11	MAR 29	No connect hour charges in WPIFV until May 1, 2004
NEWS	12	MAR 29	New monthly current-awareness alert (SDI) frequency in RAPRA

NEWS EXPRESS	MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 13 APRIL 2004
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
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FILE 'HOME' ENTERED AT 15:17:29 ON 21 APR 2004

=> FIL STNGUIDE

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'STNGUIDE' ENTERED AT 15:17:38 ON 21 APR 2004

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Apr 16, 2004 (20040416/UP).

=> FIL HOME
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.06	0.27

FILE 'HOME' ENTERED AT 15:17:44 ON 21 APR 2004

=> s goggins m?/AU OR Ueki T/au
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> file .biotech caplus
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	1.05	1.32

FILES 'MEDLINE, BIOTECHDS, EMBASE, BIOSIS, SCISEARCH, CANCERLIT, CAPLUS' ENTERED AT 15:20:43 ON 21 APR 2004

7 FILES IN THE FILE LIST

=> s goggins m?/AU OR Ueki T/au
L1 1509 GOGGINS M?/AU OR UEKI T/AU

=> s preproenkephalin or ppENK or met5-enkephalin
L2 7576 PREPROENKEPHALIN OR PPENK OR MET5-ENKEPHALIN

=> s methyla? or hypermethylation or differentially methyla?
L3 456587 METHYLA? OR HYPERMETHYLATION OR DIFFERENTIALLY METHYLA?

=> s pancreatic cancer or colorectal cancer or colon cancer
L4 227492 PANCREATIC CANCER OR COLORECTAL CANCER OR COLON CANCER

=> s l4 and l3
L5 3628 L4 AND L3

=> s l5 and l2
L6 17 L5 AND L2

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7 10 DUP REM L6 (7 DUPLICATES REMOVED)

=> d ibib abs l7 1-10

L7 ANSWER 1 OF 10 MEDLINE on STN
ACCESSION NUMBER: 2003292753 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12673125
TITLE: In search of an early warning system for **pancreatic cancer**.
COMMENT: Comment on: Cancer Biol Ther. 2003 Jan-Feb;2(1):78-83. PubMed ID: 12673124
AUTHOR: Hingorani Sunil R; Tuveson David A
CORPORATE SOURCE: Departments of Cancer Biology and Medicine, Abromson Family Cancer Research Institute, University of Pennsylvania Medical Center, Philadelphia, PA 19104, USA.. srhingo@mail.med.upenn.edu

SOURCE: Cancer biology & therapy, (2003 Jan-Feb) 2 (1) 84-6.
Journal code: 101137842. ISSN: 1538-4047.
PUB. COUNTRY: United States
DOCUMENT TYPE: Commentary
Editorial
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030625
Last Updated on STN: 20030724
Entered Medline: 20030723

L7 ANSWER 2 OF 10 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:1059067 SCISEARCH
THE GENUINE ARTICLE: 748GQ
TITLE: Comparison of epigenetic and genetic alterations in mucinous cystic neoplasm and serous microcystic adenoma of pancreas
AUTHOR: Kim S G; Wu T T; Lee J H; Yuri Y K; Issa J P; Hamilton S R; Rashid A (Reprint)
CORPORATE SOURCE: Univ Texas, MD Anderson Canc Ctr, Dept Pathol, 1515 Holcombe Blvd, Box 85, Houston, TX 77030 USA (Reprint); Univ Texas, MD Anderson Canc Ctr, Dept Pathol, Houston, TX 77030 USA; Univ Texas, MD Anderson Canc Ctr, Dept Leukemia, Houston, TX 77030 USA; Kyung Pook Natl Univ Hosp, Dept Surg, Taegu, South Korea
COUNTRY OF AUTHOR: USA; South Korea
SOURCE: MODERN PATHOLOGY, (NOV 2003) Vol. 16, No. 11, pp. 1086-1094.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
ISSN: 0893-3952.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 43

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Mucinous cystic neoplasms and serous microcystic adenomas account for the majority of cystic tumors of pancreas. Mucinous cystic neoplasms and serous microcystic adenomas have different frequencies of progression to malignancy. The genetic and epigenetic alterations of these tumors have not been studied in detail. In this study, we compared **methylation** status of p16, p14, VHL, and **ppENK** genes by **methylation** -specific PCR (MSP), and genetic alterations including K-ras and beta-catenin gene mutations, chromosome 3p loss, and microsatellite instability in 15 mucinous cystic neoplasms (10 benign and 5 borderline) and 16 serous microcystic adenomas. There were no significant differences between mucinous cystic neoplasms and serous microcystic adenomas in **methylation** of p16 (14%, 2/14 and 12%, 2/16), p14 (15%, 2/13 and 37%, 6/16), VHL (0/14 and 7%, 1/14), and **ppENK** (0/14 and 0/13), respectively. K-ras mutation was present only in mucinous cystic neoplasms but not in serous microcystic adenomas (33%, 5/15 versus 0/16; P =.004). In addition, LOH at 3p25, the chromosomal location of VHL gene, was present in 57% (8/14) of serous microcystic adenomas compared with in 17% (2/12) of mucinous cystic neoplasms (P =.03). No beta-catenin mutation, microsatellite instability, or mutation of transforming growth factor beta type II receptor was present in either type of tumors. In conclusion, K-ras mutations and allelic loss of VHL locus at 3p25, but not **methylation**, distinguished mucinous cystic neoplasms and serous microcystic adenomas. The differences in genetic alterations but not epigenetic alterations may explain the pathogenesis and progression to malignancy of these cystic tumors of pancreas.

L7 ANSWER 3 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:451805 BIOSIS

DOCUMENT NUMBER: PREV200300451805
TITLE: Multiplex oligonucleotide microarray analysis of **pancreatic cancer**.
AUTHOR(S): Kim, Yong-Tae [Reprint Author]; Moon, Woo-Chul; Uhm, Tae Han; Oh, Myung Ryul; Yoon, Yong Bum
CORPORATE SOURCE: Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 496. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Oct 2003
Last Updated on STN: 1 Oct 2003

L7 ANSWER 4 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:451568 BIOSIS
DOCUMENT NUMBER: PREV200300451568
TITLE: Is aberrant promoter **hypermethylation** of p16 and **ppENK** genes in **pancreatic cancer** related to environmental exposure?.
AUTHOR(S): Jiao, Li [Reprint Author]; Zhu, Jijiang; Hassan, Manal; Connor, Thomas H.; Issa, Jean-Pierre; Abbruzzese, James L.; Wolff, Robert A.; Lenzi, Renato; Evans, Douglas; Pister, Peter W.; Nooka, Ajay; Li, Donghui
CORPORATE SOURCE: University of Texas MD Anderson Cancer Center, Houston, TX, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 431. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Oct 2003
Last Updated on STN: 1 Oct 2003

L7 ANSWER 5 OF 10 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:451565 BIOSIS
DOCUMENT NUMBER: PREV200300451565
TITLE: CpG island **methylation** in oligodendrogliomas.
AUTHOR(S): Rey, Juan A. [Reprint Author]; Alonso, Eva; Lomas, Jesus; Arjona, Dolores; Gonzalez-Gomez, Pilar; de Campos, Jose M.; Vaquero, Jesus; Sarasa, Jose L.; Bello, Josefa
CORPORATE SOURCE: Dpt. C. Experimental, Lab. Oncogenetica Molecular, Hospital La Paz, Madrid, Spain
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 430. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Oct 2003
Last Updated on STN: 1 Oct 2003

L7 ANSWER 6 OF 10 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003156871 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12673124
TITLE: Diagnosing **pancreatic cancer** using **methylation** specific PCR analysis of pancreatic juice.
COMMENT: Comment in: Cancer Biol Ther. 2003 Jan-Feb;2(1):84-6. PubMed ID: 12673125
AUTHOR: Fukushima Noriyoshi; Walter Kimberly M; Uek Takashi; Sato Norihiro; Matsubayashi Hiroyuki; Cameron John L; Hruban Ralph H; Canto Marcia; Yeo Charles J; Goggins Michael
CORPORATE SOURCE: Department of' Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland 21205-2196, USA.
CONTRACT NUMBER: CA62924 (NCI)
SOURCE: Cancer biology & therapy, (2003 Jan-Feb) 2 (1) 78-83. Journal code: 101137842. ISSN: 1538-4047.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030404
Last Updated on STN: 20030724
Entered Medline: 20030723

AB The aim of this study was to determine the utility of detecting **methylated ppENK** and pi6 in pancreatic juice by **methylation** specific PCR as a marker of pancreatic adeno-carcinoma. Pancreatic juice samples were collected either intraoperatively, from 92 patients undergoing pancreaticoduodenectomy for benign (n=20) and malignant periampullary disease (n = 72) or endoscopically (by duodenal aspiration after secretin infusion), from 13 patients undergoing investigation for pancreatic disease. **Methylated ppENK** was detected in the pancreatic juice of 30 (66.7%) of 45 patients with pancreatic ductal adenocarcinoma, in 4 (44.4%) of 9 patients with intraductal papillary-mucinous adenocarcinoma, and in 7 (41.2%) of 17 patients with other periampullary carcinomas, using **methylation** specific PCR. **Methylated** pi6 was detected in a lower percentage of these patients (11.1%, 11.1% and 23.5%, respectively). In contrast, **methylated ppENK** and pi6 were not detected in 20 patients with non-malignant periampullary disease including 12 patients with chronic pancreatitis. **Methylated ppENK** was detected in 30 of 33 (90.9%) primary pancreatic adenocarcinoma and **methylated** pi6 was in 6/33 (1 8.2%). Despite the absence of ppENKand pi6 **methylation** in normal pancreas, **methylated ppENK** and pi6 was present in the duodenum of 90.5% and 28.6%, respectively of patients without cancer. Further, **methylated ppENK** and pi6 was seen in 88.9% and 11.1%, respectively of pancreatic juice samples obtained by duodenal aspiration from patients without cancer. We conclude that since **ppENK** and pi6 are not normally **methylated** in pancreatic secretions, detection of **methylated ppENK** and pi6 in pure pancreatic juice obtained by direct cannulation of the pancreatic duct to avoid duodenal secretions may suggest the presence of pancreatic adenocarcinoma

L7 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:676233 CAPLUS
DOCUMENT NUMBER: 137:211903
TITLE: **Differentially methylated** sequences in human **pancreatic cancer** and use in diagnosis
INVENTOR(S): Goggins, Michael G.; Ueki, Takashi
PATENT ASSIGNEE(S): The Johns Hopkins University School of Medicine, USA
SOURCE: PCT Int. Appl., 73 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002068694	A1	20020906	WO 2002-US5681	20020225
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003190616	A1	20031009	US 2002-84555	20020225
EP 1379691	A1	20040114	EP 2002-721150	20020225
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2001-271268P P 20010223
WO 2002-US5681 W 20020225

AB The present invention relates to a method of determining the DNA **methylation** status of CpG sites in a given locus and correlating the **methylation** status with the presence of a cell proliferative disorder. The method includes contacting a nucleic acid-containing specimen from the subject with an agent that provides a determination of the **methylation** state of at least one gene or associated regulatory region of the gene and identifying aberrant **methylation** of regions of the gene or regulatory region, wherein aberrant **methylation** is identified as being different when compared to the same regions of the gene or associated regulatory region in a subject not having said cellular proliferative, thereby detecting a cellular proliferative disorder in the subject. The method includes multiplexing by utilizing a combination of primers for more than one loci, thereby providing a **methylation** profile for more than one gene or regulatory region. Determining the **methylation** state of the gene includes contacting the nucleic acid-containing specimen with an agent that modifies unmethylated cytosine, amplifying a CpG-containing nucleic acid in the specimen by means of CpG-specific oligonucleotide primers, wherein the oligonucleotide primers distinguish between modified **methylated** and nonmethylated nucleic acid, and detecting the **methylated** nucleic acid based on the presence or absence of amplification products produced in said amplifying step. The method includes optionally contacting the amplification products with a **methylation** sensitive restriction endonuclease. To identify CpG islands **differentially methylated** in pancreatic adenocarcinoma, **methylated** CpG island amplification (MCA) was used, coupled with representational difference anal. (MCA/RDA). Clones **differentially methylated** (termed MICP, **methylated** in carcinoma of the pancreas) were isolated in a panel of 8 **pancreatic cancer** cell lines compared to normal pancreas. 95 % of these clones were CpG islands and among these clones were 5' CpG islands of several known genes, including Cyclin G and **Preproenkephalin** [**ppENK**, encoding (**Met5**)-**enkephalin**]. For the first time, the invention provides **methylated** forms of genes and/or their associated regulatory sequences referred to herein as MICP1-42. MICP39-42 have no homol. to known human sequences. Eleven clones matched human genes (MICPI-11); 10 clones matched human ESTs (MICP12-21); 5 clones matched human CpG islands (MICP22-26); and 12 clones matched human genome sequences (MICP27-38).

(see Table 1 as reference).
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 10 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002221119 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11960385
TITLE: Aberrant CpG island **methylation** in cancer cell lines arises in the primary cancers from which they were derived.
AUTHOR: Ueki Takashi; Walter Kimberly M; Skinner Halcyon; Jaffee Elizabeth; Hruban Ralph H; Goggins Michael
CORPORATE SOURCE: Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland, MD 21205-2196, USA.
CONTRACT NUMBER: CA62924 (NCI)
SOURCE: Oncogene, (2002 Mar 27) 21 (13) 2114-7.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020418
Last Updated on STN: 20020511
Entered Medline: 20020510

AB A higher prevalence of epigenetic inactivation of tumor suppressor genes has been reported in cancer cell line populations compared to primary cancer populations. Cancer-related genes are commonly **methylated** in cancer cell lines but it is not known the extent to which tumor suppressor genes may be artificially **methylated** in vitro. We therefore examined 10 **pancreatic cancer** cell lines and corresponding primary tumors for aberrant DNA **methylation** of promoter CpG islands of eight genes and seven CpG islands. Using **methylation**-specific PCR (MSP), **methylation** was not detected at any of the 15 CpG islands in 15 normal pancreata or in an immortalized normal pancreatic duct epithelial (HPDE) cell line. Of 150 loci examined, 49 loci were **methylated** in both primary carcinomas and their corresponding cell lines, 95 loci were not **methylated** in either cell lines or their corresponding primary carcinomas. There were four loci **methylated** only in cell lines while another two loci were **methylated** only in primary carcinomas. Overall, the **methylation** status of primary carcinomas and their cell lines were concordant in 96% of cases (144 of 150) (J statistic; J=0.92, P<0.0001). We conclude that most of the DNA **methylation** of tumor suppressor genes observed in cancer cell lines is present in the primary carcinomas from which they were derived.

L7 ANSWER 9 OF 10 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2001689479 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11731440
TITLE: Identification and characterization of **differentially methylated** CpG islands in pancreatic carcinoma.
AUTHOR: Ueki T; Toyota M; Skinner H; Walter K M; Yeo C J; Issa J P; Hruban R H; Goggins M
CORPORATE SOURCE: Department of Pathology, Johns Hopkins School of Medicine and the Johns Hopkins School of Public Health, Baltimore, Maryland 21205, USA.
CONTRACT NUMBER: 5P50CA62924-07 (NCI)
SOURCE: Cancer research, (2001 Dec 1) 61 (23) 8540-6.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011212
Last Updated on STN: 20020125
Entered Medline: 20020103

AB To identify CpG islands **differentially methylated** in pancreatic adenocarcinoma, we used **methylated** CpG island amplification (MCA) coupled with representational difference analysis. Of 42 CpG islands identified by MCA/representational difference analysis, 7 CpG islands [**methylated** in carcinoma of the pancreas (MICP)] were **differentially methylated** in a panel of eight **pancreatic cancer** cell lines compared with normal pancreas. In a larger panel of 75 pancreatic adenocarcinomas, these 7 MICPs (**ppENK**, Cyclin G, ZBP, MICP25, 27, 36, and 38) were **methylated** in 93, 3, 9, 15, 48, 19, and 41% of cancers, respectively, by **methylation**-specific PCR but not in any of 15 normal pancreata. In **pancreatic cancer** cell lines, **methylation** of **ppENK**, a gene with known growth suppressive properties, was associated with transcriptional silencing that was reversible with 5-aza-2'-deoxycytidine treatment. Relationships between the **methylation** patterns of pancreatic adenocarcinomas and their clinicopathological features were also determined. Larger pancreatic cancers and those from older patients (P = 0.017) harbored more **methylated** loci than smaller tumors and those from younger patients (P = 0.017). **ppENK**, MICP25, and 27 were variably **methylated** in normal gastric, duodenal, and colonic mucosae. These data indicate that aberrant **methylation** of **ppENK** and its transcriptional repression is a common event in pancreatic carcinogenesis.

L7 ANSWER 10 OF 10 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 96301179 EMBASE
DOCUMENT NUMBER: 1996301179
TITLE: Opioid growth factor tonically inhibits human **colon cancer** cell proliferation in tissue culture.
AUTHOR: Zagon I.S.; Hytrek S.D.; McLaughlin P.J.
CORPORATE SOURCE: Dept. of Neuroscience and Anatomy, M. S. Hershey Medical Center, Pennsylvania State Univ., 500 University Dr.,Hershey, PA 17033, United States
SOURCE: American Journal of Physiology - Regulatory Integrative and Comparative Physiology, (1996) 271/3 40-3 (R511-R518). ISSN: 0363-6119 CODEN: AJPRDO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Native opioid peptides serve as growth factors in a number of normal and neoplastic cells and tissues, including the prevention and delayed growth of human **colon cancer** xenografts in nude mice. This study examined the hypothesis that opioids exert a direct inhibitory influence on tumor cell growth by the use of a tissue culture model. The naturally occurring pentapeptide [**Met5**]**enkephalin** depressed growth of HT-29 human **colon cancer** cells from 17 to 41% at 12-72 h after administration of 10-6 M concentration; consistent with previously defined nomenclature, this peptide was termed opioid growth factor (OGF). OGF action exhibited a dose-response relationship, was reversible and not cytotoxic, and was opioid receptor mediated. Growth inhibition by OGF was not dependent on serum, and was noted in the two other human **colon cancer** cell lines examined, WiDr and COLO 205. This peptide continually repressed growth

because an increase in cell number was noted when cells were exposed to the potent opioid antagonist naltrexone or an antibody to OGF. Both OGF and its receptor, zeta (ζ), were found in **colon cancer** cells by immunocytochemistry, and receptor binding assays revealed a nuclear-associated receptor with a dissociation constant of 8.9 nM and a maximum binding capacity of 43 fmol/mg of protein. OGF was produced and secreted by the tumor cells. These results lead to the suggestion that OGF has a direct, tonic, inhibitory action on the growth of human **colon cancer** cells and contribute to our understanding of the mechanisms underlying the marked antitumor effect of this peptide in nude mice inoculated with human **colon cancer** cells.

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=> d his

     (FILE 'HOME' ENTERED AT 15:17:29 ON 21 APR 2004)

     FILE 'STNGUIDE' ENTERED AT 15:17:38 ON 21 APR 2004

     FILE 'HOME' ENTERED AT 15:17:44 ON 21 APR 2004

     FILE 'MEDLINE, BIOTECHDS, EMBASE, BIOSIS, SCISEARCH, CANCERLIT, CAPLUS'
     ENTERED AT 15:20:43 ON 21 APR 2004
L1          1509 S GOGGINS M?/AU OR UEKI T/AU
L2          7576 S PREPROENKEPHALIN OR PPENK OR MET5-ENKEPHALIN
L3        456587 S METHYLA? OR HYPERMETHYLATION OR DIFFERENTIALLY METHYLA?
L4        227492 S PANCREATIC CANCER OR COLORECTAL CANCER OR COLON CANCER
L5          3628 S L4 AND L3
L6            17 S L5 AND L2
L7            10 DUP REM L6 (7 DUPLICATES REMOVED)

=> s l1 and l3
L8           123 L1 AND L3

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9            44 DUP REM L8 (79 DUPLICATES REMOVED)

=> s l9 and l4
L10          24 L9 AND L4

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11           24 DUP REM L10 (0 DUPLICATES REMOVED)

=> d ibib abs l11 1-24

L11  ANSWER 1 OF 24     MEDLINE on STN
ACCESSION NUMBER:   2004096000     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 14716296
TITLE:              Identification of maspin and S100P as novel hypomethylation
                    targets in pancreatic cancer using
                    global gene expression profiling.
AUTHOR:             Sato Norihiro; Fukushima Noriyoshi; Matsubayashi Hiroyuki;
                    Goggins Michael
CORPORATE SOURCE:   1Department of Pathology, The Johns Hopkins Medical
                    Institutions, Baltimore, MD, USA.
CONTRACT NUMBER:    CA62924 (NCI)
     CA90709 (NCI)
SOURCE:             Oncogene, (2004 Feb 26) 23 (8) 1531-8.
                    Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY:       England: United Kingdom
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
```

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200403
ENTRY DATE: Entered STN: 20040302
Last Updated on STN: 20040319
Entered Medline: 20040318

AB DNA hypomethylation is one of the major epigenetic alterations in human cancers. We have previously shown that genes identified as hypomethylated in **pancreatic cancer** are expressed in **pancreatic cancer** cell lines, but not in normal pancreatic ductal epithelium and can be reexpressed in nonexpressing cells using 'epigenetic modifying agents' such as DNA methyltransferase inhibitors. To identify additional targets for aberrant hypomethylation in **pancreatic cancer**, we used oligonucleotide microarrays to screen for genes that displayed expression patterns associated with hypomethylation. This analysis identified a substantial number of candidates including previously reported hypomethylated genes. A subset of eight genes were selected for further **methylation** analysis, and two cancer-related genes, maspin and S100P, were found to be aberrantly hypomethylated in a large fraction of **pancreatic cancer** cell lines and primary pancreatic carcinomas. Combined treatment with 5-aza-2'-deoxycytidie and trichostatin A resulted in synergistic induction of maspin and S100P mRNA in MiaPaCa2 cells where both genes were **methylated**. Furthermore, there was an inverse correlation between **methylation** and mRNA expression level for maspin and S100P in a large panel of **pancreatic cancer** cell lines. We also found a significant difference in the **methylation** patterns of maspin and two previously identified hypomethylated genes (trefoil factor 2 and lipocalin 2) between pancreatic and breast cancer cell lines, suggesting cancer-type specificity for some hypomethylation patterns. Thus, our present results confirm that DNA hypomethylation is a frequent epigenetic event in **pancreatic cancer**, and suggest that gene expression profiling may help to identify potential targets affected by this epigenetic alteration.

L11 ANSWER 2 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2003368577 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12902985
TITLE: SPARC/osteonectin is a frequent target for aberrant **methylation** in pancreatic adenocarcinoma and a mediator of tumor-stromal interactions.
AUTHOR: Sato Norihiro; Fukushima Noriyoshi; Maehara Naoki; Matsubayashi Hiroyuki; Koopmann Jens; Su Gloria H; Hruban Ralph H; **Goggins Michael**
CORPORATE SOURCE: Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, MD, USA.
CONTRACT NUMBER: CA62924 (NCI)
SOURCE: Oncogene, (2003 Aug 7) 22 (32) 5021-30.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 20030807
Last Updated on STN: 20030917
Entered Medline: 20030916

AB Deregulated expression of SPARC/osteonectin, a secreted glycoprotein with multiple biological functions, has been associated with the progression of various cancers. Using microarrays, we previously identified SPARC as one of the genes induced by treatment with a DNA **methylation** inhibitor in **pancreatic cancer** cells. We therefore analysed the expression pattern and **methylation** status of the SPARC gene in **pancreatic cancer**. Gene expression

profiling by oligonucleotide microarray and reverse transcription-PCR analyses demonstrated that SPARC mRNA was expressed in non-neoplastic pancreatic ductal epithelial cells, but was not expressed in a majority of **pancreatic cancer** cell lines. The loss of SPARC expression was associated with aberrant **hypermethylation** of its CpG island. Immunohistochemical labeling revealed that the SPARC protein was overexpressed in the stromal fibroblasts immediately adjacent to the neoplastic epithelium in primary pancreatic cancers, but rarely expressed in the cancers themselves. Primary fibroblasts derived from **pancreatic cancer** strongly expressed SPARC mRNA and secreted SPARC protein into the conditioned media, and treatment of **pancreatic cancer** cells with exogenous SPARC resulted in growth suppression. SPARC expression in fibroblasts from noncancerous pancreatic tissue was augmented by coculture with **pancreatic cancer** cells. These findings suggest that SPARC is a frequent target for aberrant **methylation** in **pancreatic cancer** and that SPARC expression in fibroblasts adjacent to **pancreatic cancer** cells is regulated through tumor-stromal interactions.

L11 ANSWER 3 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2003341672 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12874021
TITLE: Frequent hypomethylation of multiple genes overexpressed in pancreatic ductal adenocarcinoma.
AUTHOR: Sato Norihiro; Maitra Anirban; Fukushima Noriyoshi; van Heek N Tjarda; Matsubayashi Hiroyuki; Iacobuzio-Donahue Christine A; Rosty Christophe; **Goggins Michael**
CORPORATE SOURCE: Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland 21205, USA.
CONTRACT NUMBER: CA62924 (NCI)
CA90709 (NCI)
SOURCE: Cancer research, (2003 Jul 15) 63 (14) 4158-66.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030723
Last Updated on STN: 20030814
Entered Medline: 20030813

AB To investigate the relationship between DNA hypomethylation and gene overexpression in **pancreatic cancer**, we analyzed the **methylation** status of a subset of 18 genes previously identified by global gene expression studies as overexpressed in **pancreatic cancer** tissues compared with normal pancreas. For comparison, we determined the **methylation** status of 14 genes not known to be overexpressed in **pancreatic cancer**. **Methylation**-specific PCR analysis revealed that 19 of these 32 genes were **methylated** at their 5' CpGs in normal pancreas. We then analyzed these 19 genes for their **methylation** pattern in pancreatic cancers and found that all 7 of the genes (claudin4, lipocalin2, 14-3-3sigma, trefoil factor2, S100A4, mesothelin, and prostate stem cell antigen) that were overexpressed in the neoplastic cells of pancreatic cancers and not expressed in normal pancreatic duct displayed a high prevalence of hypomethylation in **pancreatic cancer** cell lines and primary pancreatic carcinomas. By contrast, only 1 of 12 genes not overexpressed in **pancreatic cancer** demonstrated hypomethylation (P = 0.0002). In **pancreatic cancer** cell lines that retained **methylation** of 1 or more of the 7 aforementioned overexpressed and hypomethylated genes, treatment with 5-aza-2'-deoxycytidine or with trichostatin A, either alone or in combination, almost invariably reactivated the transcription of each of

these 7 genes. These results indicate that gene hypomethylation is a frequent epigenetic event in **pancreatic cancer** and is commonly associated with the overexpression of affected genes.

L11 ANSWER 4 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2003311519 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12839967
TITLE: Discovery of novel targets for aberrant **methylation** in pancreatic carcinoma using high-throughput microarrays.
AUTHOR: Sato Norihiro; Fukushima Noriyoshi; Maitra Anirban; Matsubayashi Hiroyuki; Yeo Charles J; Cameron John L; Hruban Ralph H; **Goggins Michael**
CORPORATE SOURCE: Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland 21205-2196, USA.
CONTRACT NUMBER: CA69294 (NCI)
SOURCE: Cancer research, (2003 Jul 1) 63 (13) 3735-42. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030704
Last Updated on STN: 20030826
Entered Medline: 20030825

AB To identify potential targets for aberrant **methylation** in **pancreatic cancer**, we analyzed global changes in gene expression profiles of four **pancreatic cancer** cell lines after treatment with the demethylating agent 5-aza-2'-deoxycytidine (5Aza-dC) and/or the histone deacetylase inhibitor trichostatin A. A substantial number of genes were induced 5-fold or greater by 5Aza-dC alone (631 transcripts), trichostatin A alone (1196 transcripts), and by treatment with both agents (857 transcripts). Four hundred and seventy-five genes were markedly (>5-fold) induced after 5Aza-dC treatment in **pancreatic cancer** cell lines but not in a nonneoplastic pancreatic epithelial cell line. The **methylation** status of 11 of these 475 genes was examined in a panel of 42 pancreatic cancers, and all 11 of these genes were aberrantly **methylated** in **pancreatic cancer** but rarely, if any, **methylated** in 10 normal pancreatic ductal epithelia. These genes include UCHL1 (**methylated** in 100% of 42 pancreatic cancers), NPTX2 (98%), SARP2 (95%), CLDN5 (93%), reprimo (86%), LHX1 (76%), WNT7A (71%), FOXE1 (69%), TJP2 (64%), CDH3 (19%), and ST14 (10%). Three of these 11 genes (NPTX2, SARP2, and CLDN5) were selected for further analysis in a larger panel of specimens, and aberrant **methylation** of at least one of these three genes was detectable in 100% of 43 primary pancreatic cancers and in 18 of 24 (75%) pancreatic juice samples obtained from patients with **pancreatic cancer**. Thus, a substantial number of genes are induced by 5Aza-dC treatment of **pancreatic cancer** cells, and many of them may represent novel targets for aberrant **methylation** in pancreatic carcinoma.

L11 ANSWER 5 OF 24 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:1045744 SCISEARCH
THE GENUINE ARTICLE: 747TH
TITLE: p16 inactivation in pancreatic intraepithelial neoplasias (PanINs) arising in patients with chronic pancreatitis
AUTHOR: Rosty C; Geradts J; Sato N; Wilentz R E; Roberts H; Sohn T; Cameron J L; Yeo C J; Hruban R H; **Goggins M (Reprint)**
CORPORATE SOURCE: Johns Hopkins Med Inst, Dept Pathol, 632 Ross Bldg, 720 Rutland Ave, Baltimore, MD 21205 USA (Reprint); Johns Hopkins Med Inst, Dept Pathol, Baltimore, MD 21205 USA; Johns Hopkins Med Inst, Dept Oncol, Baltimore, MD 21205

USA; Johns Hopkins Med Inst, Dept Surg, Baltimore, MD 21205 USA; Johns Hopkins Med Inst, Dept Med, Baltimore, MD 21205 USA; Roswell Pk Canc Inst, Dept Pathol & Lab Med, Buffalo, NY 14263 USA; Univ Oxford, Nuffield Dept Clin Lab Sci, Oxford OX1 2JD, England; Inst Curie, Dept Pathol, Paris, France

COUNTRY OF AUTHOR: USA; England; France
SOURCE: AMERICAN JOURNAL OF SURGICAL PATHOLOGY, (DEC 2003) Vol. 27, No. 12, pp. 1495-1501.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
ISSN: 0147-5185.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 27

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Patients with long-standing chronic pancreatitis are thought to be at increased risk of developing pancreatic ductal adenocarcinoma, but the mechanism for this increased risk is unknown. Since increasing evidence supports the notion that infiltrating pancreatic ductal adenocarcinomas arise from pancreatic intraepithelial lesions (PanINs), we sought to determine if patients with chronic pancreatitis harbor PanINs with alterations in tumor suppressor genes that are associated with infiltrating pancreatic ductal adenocarcinoma. We identified 122 patients with a diagnosis of chronic pancreatitis and 29 patients with a well-differentiated pancreatic endocrine tumor that underwent pancreatic surgery at the Johns Hopkins Hospital from 1985 to 1999. PanINs from each resection specimen were identified, graded, counted, and correlated with smoking and alcohol history. The expression patterns of p 16 and Smad4 were determined in a subset of PanINs by immunohistochemistry, and the pattern of labeling compared with that seen in PanINs associated with infiltrating adenocarcinoma of the pancreas as identified in prior studies, and to PanfNs associated with pancreatic endocrine tumor. Duct lesions were present in 80 of the 122 pancreata with chronic pancreatitis (66%). Of 405 duct lesions identified in the chronic pancreatitis group, 7.6% were reactive changes, 65.5% were PanIN-1A, 18% werePanIN-1B, 7.4%were PanIN-2,and 1.5% were PanIN-3. Within the pancreatic endocrine tumor group, 22 PanfNs were identified: 15 PanIN-1A, 4 PanIN-1B, and 3 PanIN-2. There were significantly fewer high-grade PanfNs in the pancreata with chronic pancreatitis than in pancreata with pancreatic adenocarcinoma ($P < 0.0001$). Within the chronic pancreatitis group, the 80 patients with PanINs were significantly older than the 42 patients without PanfNs (mean age 57.0 +/- 14.1 years vs. 50.9 +/- 14.7 years, $P = 0.01$). Smoking history was not associated with PanIN prevalence or grade, but patients who reported a history of excessive alcohol consumption had fewer PanINs (25 of 44 harbored PanINs, 57%) than those who did not (54 of 74, 73%, $P = 0.07$). In the chronic pancreatitis group, 0% of PanIN-1A, 11% of the PanIN-1B, 16% of the PanIN-2, and 40% of the PanIN-3 lesions showed loss of p16 expression, whereas all of the PanINs from patients with an pancreatic endocrine tumor retained p16 expression. All of the PanINs analyzed from patients with chronic pancreatitis retained normal Smad4 expression. We conclude that a significant minority of PanINs arising in patients with chronic pancreatitis show loss of p16 expression. This alteration, common to **pancreatic cancer**-associated PanINs, may contribute to the predisposition of patients with chronic pancreatitis to develop pancreatic ductal adenocarcinoma.

L11 ANSWER 6 OF 24 MEDLINE on STN

ACCESSION NUMBER: 2003174797 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12684418

TITLE: **Methylation** of cyclin D2 is observed frequently in **pancreatic cancer** but is also an age-related phenomenon in gastrointestinal tissues.

AUTHOR: Matsubayashi Hiroyuki; Sato Norihiro; Fukushima Noriyoshi;

Yeo Charles J; Walter Kimberly M; Brune Kieran; Sahin Fikret; Hruban Ralph H; **Goggins Michael**

CORPORATE SOURCE: Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland, 21205-2196, USA.

CONTRACT NUMBER: CA62924 (NCI)
SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (2003 Apr) 9 (4) 1446-52.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200401
ENTRY DATE: Entered STN: 20030417
Last Updated on STN: 20040121
Entered Medline: 20040120

AB PURPOSE: **Hypermethylation** of CpG islands in the promoters of selected genes is a common feature of neoplasia. Aberrant **methylation** of cyclin D2 has been observed in several cancers. We investigated the **methylation** of cyclin D2 in aging and pancreatic neoplastic development, and the utility of cyclin D2 **methylation** as a marker of pancreatic adenocarcinoma. EXPERIMENTAL DESIGN: **Methylation**-specific PCR was performed on DNA from 165 resected pancreatic exocrine neoplasms [109 adenocarcinomas, 46 intraductal papillary-mucinous neoplasms (IPMNs), and 10 mucinous cystic neoplasms], 14 pancreatic intraepithelial neoplasms, 13 microdissected-normal pancreatic ductal epithelia, 25 normal pancreatic parenchyma, 51 specimens of pancreatic juice obtained perioperatively, 15 **pancreatic cancer** xenografts, 22 **pancreatic cancer** cell lines, 59 specimens of normal duodenum, and 49 gallbladders affected by cholecystitis. Cyclin D2 RNA expression was determined in **pancreatic cancer** cell lines, before and after 5-AZA-2'-deoxycytidine treatment, by reverse transcription-PCR. RESULTS: **Methylation** of cyclin D2 was identified in 65.1% (71 of 109) of primary pancreatic adenocarcinomas, in 50% (23 of 46) of IPMNs, and in 70% (7 of 10) of mucinous cystic neoplasms, but was detected infrequently in microdissected samples of normal pancreatic epithelia [7.7% (1 of 13)] and in pancreatic intraepithelial neoplasms [14.3% (2 of 14)]. Cyclin D2 **methylation** was also recognized in 10 of 15 (66.7%) **pancreatic cancer** xenografts and in 19 of 22 (86.4%) **pancreatic cancer** cell lines. All of 10 **pancreatic cancer** cell lines completely **methylated** at cyclin D2 showed no expression by reverse transcription-PCR. Four of these 10 cell lines were treated with 5-AZA-2'-deoxycytidine, and all 4 showed increased RNA expression of cyclin D2 after treatment. In pancreatic juice, cyclin D2 **methylation** was detected in 9 of 22 (40.9%) samples from patients with **pancreatic cancer** and in 6 of 9 (66.7%) patients with IPMNs, but in none of 20 non-neoplastic controls, respectively ($P = 0.0013$ and $P < 0.0001$, respectively). **Methylation** of cyclin D2 was also observed more in non-neoplastic tissues and with increasing age ($P = 0.041$ in the pancreas, $P = 0.047$ in the duodenum, and $P = 0.0008$ in the gallbladder). CONCLUSIONS: The promoter region of cyclin D2 undergoes age-related **methylation** in multiple tissues, but aberrant **methylation** is more often detected in tissues and juice samples of **pancreatic cancer** than in normal tissues. The detection of cyclin D2 **methylation** in pancreatic juice may aid in the diagnosis of pancreatic adenocarcinoma.

L11 ANSWER 7 OF 24 MEDLINE on STN

ACCESSION NUMBER: 2003136352 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12651607

TITLE: Exploration of global gene expression patterns in

pancreatic adenocarcinoma using cDNA microarrays.
AUTHOR: Iacobuzio-Donahue Christine A; Maitra Anirban; Olsen Mari; Lowe Anson W; van Heek N Tjarda; Rosty Christophe; Walter Kim; Sato Norihiro; Parker Antony; Ashfaq Raheela; Jaffee Elizabeth; Ryu Byungwoo; Jones Jessa; Eshleman James R; Yeo Charles J; Cameron John L; Kern Scott E; Hruban Ralph H; Brown Patrick O; **Goggins Michael**
CORPORATE SOURCE: Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland 21205, USA.
CONTRACT NUMBER: CA62924 (NCI)
CA85129 (NCI)
SOURCE: American journal of pathology, (2003 Apr) 162 (4) 1151-62.
Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20030325
Last Updated on STN: 20030613
Entered Medline: 20030612

AB **Pancreatic cancer** is the fifth leading cause of cancer death in the United States. We used cDNA microarrays to analyze global gene expression patterns in 14 **pancreatic cancer** cell lines, 17 resected infiltrating **pancreatic cancer** tissues, and 5 samples of normal pancreas to identify genes that are differentially expressed in **pancreatic cancer**. We found more than 400 cDNAs corresponding to genes that were differentially expressed in the **pancreatic cancer** tissues and cell lines as compared to normal pancreas. These genes that tended to be expressed at higher levels in pancreatic cancers were associated with a variety of processes, including cell-cell and cell-matrix interactions, cytoskeletal remodeling, proteolytic activity, and Ca(++) homeostasis. Two prominent clusters of genes were related to the high rates of cellular proliferation in **pancreatic cancer** cell lines and the host desmoplastic response in the resected **pancreatic cancer** tissues. Of 149 genes identified as more highly expressed in the pancreatic cancers compared with normal pancreas, 103 genes have not been previously reported in association with **pancreatic cancer**. The expression patterns of 14 of these highly expressed genes were validated by either immunohistochemistry or reverse transcriptase-polymerase chain reaction as being expressed in **pancreatic cancer**. The overexpression of one gene in particular, 14-3-3 sigma, was found to be associated with aberrant hypomethylation in the majority of pancreatic cancers analyzed. The genes and expressed sequence tags presented in this study provide clues to the pathobiology of **pancreatic cancer** and implicate a large number of potentially new molecular markers for the detection and treatment of **pancreatic cancer**.

L11 ANSWER 8 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2003332697 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12865927
TITLE: Aberrant **methylation** of suppressor of cytokine signalling-1 (SOCS-1) gene in pancreatic ductal neoplasms.
AUTHOR: Fukushima N; Sato N; Sahin F; Su G H; Hruban R H; **Goggins M**
CORPORATE SOURCE: Department of Pathology, The Johns Hopkins Medical Institutions, 632 Ross Building, 720 Rutland Ave, Baltimore, MD 21205-2196, USA.
CONTRACT NUMBER: CA62924 (NCI)
CA91968 (NCI)
SOURCE: British journal of cancer, (2003 Jul 21) 89 (2) 338-43.
Journal code: 0370635. ISSN: 0007-0920.

PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030717
Last Updated on STN: 20030830
Entered Medline: 20030829

AB The suppressor of cytokine signalling-1 (SOCS-1) gene is frequently silenced in human hepatocellular carcinoma by aberrant **methylation**. The aim of this study was to determine if SOCS-1 is inactivated in pancreatic ductal neoplasms, and to investigate if aberrant **methylation** of this gene affected the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway. Aberrant **methylation** in the CpG island of the SOCS-1 gene was detected in six of 19 (31.6%) human **pancreatic cancer** cell lines using **methylation**-specific PCR, and was associated with a loss or reduction of gene expression in five of the six **methylated** cell lines. Thirteen of 60 pancreatic ductal adenocarcinomas (21.7%) and two of 34 intraductal papillary mucinous neoplasms (IPMNs) (5.9%) had **methylated** SOCS-1. In contrast, SOCS-1 **methylation** was not seen in pancreatic normal ductal epithelia (zero out of 15), in pancreatic intraepithelial neoplasia (PanINs) (zero out of 49) or in the IPMNs without infiltrating cancer (zero out of 20). 5-Aza-2'-deoxycytidine treatment of the SOCS-1-**methylated pancreatic cancer** cell lines led to restoration of SOCS-1 gene expression. Interleukin-6, which has been shown to act through the JAK/STAT pathway to increase cell growth, induced modest time and dose-dependent cell proliferation in a SOCS-1-**methylated** cell line (PL10, P=0.015) but not in two unmethylated cell lines. These results indicate that loss of SOCS-1 gene is associated with transcriptional silencing and may have growth-promoting effects, and that its **methylation** is a useful marker of **pancreatic cancer**.

L11 ANSWER 9 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2003080391 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12591989
TITLE: Effects of 5-aza-2'-deoxycytidine on matrix metalloproteinase expression and **pancreatic cancer** cell invasiveness.
AUTHOR: Sato Norihiro; Maehara Naoki; Su Gloria H; **Goggins Michael**
CORPORATE SOURCE: Department of Pathology, The Johns Hopkins Medical Institutions, 720 Rutland Avenue, Baltimore, MD 21205, USA.
CONTRACT NUMBER: CA 62924 (NCI)
SOURCE: Journal of the National Cancer Institute, (2003 Feb 19) 95 (4) 327-30.
Journal code: 7503089. ISSN: 0027-8874.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 20030221
Last Updated on STN: 20030319
Entered Medline: 20030318

AB To investigate whether DNA **methylation** and the invasive phenotype of pancreatic adenocarcinoma are associated, we studied the role of **methylation** in the transcriptional regulation of several matrix metalloproteinases (MMPs) and the effect of 5-aza-2'-deoxycytidine (5Aza-dC), an inhibitor of DNA **methylation**, on the invasive behavior of **pancreatic cancer** cells. Using the Boyden chamber in vitro invasion assay, we found a statistically significant increase in invasive potential in four of five **pancreatic**

cancer cell lines after treatment with 5Aza-dC. This enhanced invasiveness was associated with the induction of mRNAs for one or more MMPs critical for tumor invasion, including MMP-1, -2, -3, -7, -9, and -14. Addition of an MMP inhibitor (GM6001, GM1489, doxycycline, or tissue inhibitor of metalloproteinase 2) blocked the 5Aza-dC-induced increase in the number of invading cells. As shown by a **methylation** -specific polymerase chain reaction, 5' CpG sites in MMP-2, -7, and -9 genes were partially or completely **methylated** in cell lines that expressed little or no corresponding mRNAs. Thus, DNA **methylation** influences the expression of MMP genes, and use of **methylation** inhibitors may stimulate the invasion of **pancreatic cancer** by reactivating invasion-promoting genes.

L11 ANSWER 10 OF 24 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:442056 BIOSIS
DOCUMENT NUMBER: PREV200300442056
TITLE: **Methylation** of cyclin D2 is frequently observed in **pancreatic cancer** but is also an age-related phenomenon in gastrointestinal tissues.
AUTHOR(S): Matsubayashi, Hiroyuki [Reprint Author]; Sato, Norihiro [Reprint Author]; Fukushima, Noriyoshi [Reprint Author]; Yeo, Charles J. [Reprint Author]; Walter, Kimberly M. [Reprint Author]; Brune, Kieran [Reprint Author]; Hruban, Ralph H. [Reprint Author]; Su, Gloria H. [Reprint Author]; **Goggins, Michael** [Reprint Author]
CORPORATE SOURCE: Johns Hopkins Medical Institutions, Baltimore, MD, USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 184-185. print. Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Sep 2003
Last Updated on STN: 24 Sep 2003

L11 ANSWER 11 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2003156871 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12673124
TITLE: Diagnosing **pancreatic cancer** using **methylation** specific PCR analysis of pancreatic juice.
COMMENT: Comment in: Cancer Biol Ther. 2003 Jan-Feb;2(1):84-6.
PubMed ID: 12673125
AUTHOR: Fukushima Noriyoshi; Walter Kimberly M; Uek Takashi; Sato Norihiro; Matsubayashi Hiroyuki; Cameron John L; Hruban Ralph H; Canto Marcia; Yeo Charles J; **Goggins Michael**
CORPORATE SOURCE: Department of' Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland 21205-2196, USA.
CONTRACT NUMBER: CA62924 (NCI)
SOURCE: Cancer biology & therapy, (2003 Jan-Feb) 2 (1) 78-83.
Journal code: 101137842. ISSN: 1538-4047.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030404
Last Updated on STN: 20030724
Entered Medline: 20030723
AB The aim of this study was to determine the utility of detecting

methylated ppENK and pi6 in pancreatic juice by **methylation** specific PCR as a marker of pancreatic adeno-carcinoma. Pancreatic juice samples were collected either intraoperatively, from 92 patients undergoing pancreaticoduodenectomy for benign (n=20) and malignant periampullary disease (n = 72) or endoscopically (by duodenal aspiration after secretin infusion), from 13 patients undergoing investigation for pancreatic disease. **Methylated** ppENK was detected in the pancreatic juice of 30 (66.7%) of 45 patients with pancreatic ductal adenocarcinoma, in 4 (44.4%) of 9 patients with intraductal papillary-mucinous adenocarcinoma, and in 7 (41.2%) of 17 patients with other periampullary carcinomas, using **methylation** specific PCR. **Methylated** pi6 was detected in a lower percentage of these patients (11.1%, 11.1% and 23.5%, respectively). In contrast, **methylated** ppENK and pi6 were not detected in 20 patients with non-malignant periampullary disease including 12 patients with chronic pancreatitis. **Methylated** ppENK was detected in 30 of 33 (90.9%) primary pancreatic adenocarcinoma and **methylated** pi6 was in 6/33 (1 8.2%). Despite the absence of ppENKand pi6 **methylation** in normal pancreas, **methylated** ppENK and pi6 was present in the duodenum of 90.5% and 28.6%, respectively of patients without cancer. Further, **methylated** ppENK and pi6 was seen in 88.9% and 11.1%, respectively of pancreatic juice samples obtained by duodenal aspiration from patients without cancer. We conclude that since ppENK and pi6 are not normally **methylated** in pancreatic secretions, detection of **methylated** ppENK and pi6 in pure pancreatic juice obtained by direct cannulation of the pancreatic duct to avoid duodenal secretions may suggest the presence of pancreatic adenocarcinoma

L11 ANSWER 12 OF 24 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2003-04599 BIOTECHDS
TITLE: New isolated nucleic acid molecules comprising **differentially methylated** sequences, and associated regulatory sequences, useful for cancer screening, risk-assessment, prognosis, or minimal-residual disease identification;
recombinant protein production useful for cancer diagnosis, prognosis and risk-assessment
AUTHOR: **GOGGINS M G; UEKI T**
PATENT ASSIGNEE: UNIV JOHNS HOPKINS SCHOOL MEDICINE
PATENT INFO: WO 2002068694 6 Sep 2002
APPLICATION INFO: WO 2002-US5681 25 Feb 2002
PRIORITY INFO: US 2001-271268 23 Feb 2001; US 2001-271268 23 Feb 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-707019 [76]
AN 2003-04599 BIOTECHDS
AB DERWENT ABSTRACT:
NOVELTY - An isolated nucleic acid molecule (I) comprising any of the 42 sequences of 179-585 base pairs (bp) (S1-S42), fully defined in the specification, and its associated regulatory sequences, are new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) a substantially purified polypeptide (II) encoded by the polynucleotide comprising a sequence of 304, 307 and 479 bp, fully defined in the specification; (2) a method (III) for detecting a cellular proliferative disorder in a subject; (3) a kit (IV) for the method (III) comprising: (a) a carrier means compartmentalized to receive a sample; and (b) one or more containers comprising a first container containing a reagent that modifies unmethylated cytosine and a second container containing primers for amplification of a CpG-containing nucleic acid, where the primer hybridizes with a target polynucleotide sequence of the nucleic acid molecule cited above; (4) isolated oligonucleotide primer(s) (V) for detection of a **methylated** CpG-containing nucleic acid (the primer hybridizes to (S1-S42)); and (5) an oligonucleotide primer

pairs selected from any of 63 nucleotide sequences, fully defined in the specification, e.g.: (a) 5'-GAGTTGGTGATGTTAGATTAG-3'; (b) 5'-TTCCCAAAAAAATCCCAAATTC-3'; (c) 5'-AGAGAGGAGTTTAGATTGG-3'; (d) 5'-CAAAAAAACTAAAACCTCAAC-3'; (e) 5'-ATTATTTTAGTAGAGGTATATAAG-3'; or (f) 5'-CCAACCCCACCCTTCAAC-3'.

BIOTECHNOLOGY - Preferred Nucleic Acid: The associated regulatory sequences of the nucleic acid molecule contain CpG-rich regions. The state of **methylation** of the CpG-rich regions is determinative of the presence of a cellular proliferative disorder in a subject from which the nucleic acid molecule is isolated. The **hypermethylation** of the CpG islands is indicative of the presence of cellular proliferative disorder in a subject from which the nucleic acid is isolated. The nucleic acid molecule preferably comprises a sequence of 304, 307 and 479 bp, fully defined in the specification. Preferred Method: Detecting a cellular proliferative disorder in a subject comprises: (a) contacting a nucleic acid-containing specimen from the subject with an agent that provides a determination of the **methylation** state of at least one gene or associated regulatory region of the gene selected from MCP1-42 identified in specification or their combinations; and (b) identifying aberrant **methylation** of regions of the gene or regulatory region (aberrant **methylation** is identified as different when compared to the same regions of the gene or associated regulatory region in a subject not having the cellular proliferation), therefore detecting a cellular proliferative disorder in the subject. The regions of the gene are contained within CpG rich regions. The aberrant **methylation** comprises **hypermethylation** when compared to the same regions of the gene or associated regulatory regions in a subject not having the cellular proliferative disorder. The agent is a pair of primers that hybridize with a target sequence in the gene or associated regulatory region of the gene. The nucleic acid-containing specimen comprises a tissue selected form brain, colon, urogenital, lung, renal, prostate, pancreas, liver, esophagus, stomach, hematopoietic, breast, thymus, testis, ovarian, or uterine. The specimen is selected from serum, urine, saliva, blood, duodenal fluid, pancreatic fluid, cerebrospinal fluid, pleural fluid, ascites fluid, sputum, stool or biopsy sample. The cellular proliferative disorder can be low-grade or anaplastic astrocytoma, glioblastoma, medullablastoma, gastric cancer, **colorectal cancer**, colorectal adenoma, acute myelogenous leukemia, leukemia, neuroblastoma, or lung, renal, breast, prostate or endometrial cancer. Preferred Kit: The kit further comprises a third container containing a **methylation** sensitive restriction endonuclease. The modifying agent comprised in the kit is a bisulfite. The primer hybridizes with a target polynucleotide sequence of 304, 307 and 479 bp, fully defined in the specification.

USE - The nucleic acid molecules and polypeptides are useful for cancer screening, risk-assessment, prognosis, minimal-residual disease identification, staging and identification of therapeutic targets. They are also useful in detecting cellular proliferative disorder in a patient.

EXAMPLE - **Methylated** CpG Island Amplification/Representational Difference Analysis (MCA/RDA) was performed, modifying the procedure to increase the efficiency by digesting 5 micrograms of DNA with SmaI and XmaI, The restriction fragments were then ligated to RMCA adapter and amplified by PCR (polymerase chain reaction) in 10mM Tris-HCl, 1.5 mM MgCl2, 50 mM KCl, 0.5 M betaine, 2% DMSO (dimethyl-sulfoxide), 200 microM each deoxynucleotide triphosphate, 100 pmol of RMCA 24mer primer and 15 units of Taq polymerase in a final reaction volume of 100 microliters. The reaction mixture was then incubated at 72 degrees Centigrade for 5 minutes and at 95 degrees Centigrade for 3 minutes, and then subjected to 25 cycles of 1 minute at 95 degrees Centigrade and 3 minutes at 77 degrees Centigrade followed by a final extension of 10 minutes at 77 degrees Centigrade. Betaine was included in the PCR reaction to help

amplify the **methylated** templates at a higher annealing temperature (77 degrees Centigrade). The MCA amplicon from either the **pancreatic cancer** cell line PL3 or PL8 was used as the tester for RDA, and a MCA amplicon generated from a mixture of DNA from the normal pancreata of six different patients was used as the driver. RDA was performed on these MCA amplicons using different adapters, JMCA and NMCA. After the third round of competitive hybridization and selective amplification, the RDA difference products of second and third round amplifications were cloned into pBluescript II plasmid vector.(73 pages)

L11 ANSWER 13 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2002221119 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11960385
TITLE: Aberrant CpG island **methylation** in cancer cell lines arises in the primary cancers from which they were derived.
AUTHOR: Ueki Takashi; Walter Kimberly M; Skinner Halcyon; Jaffee Elizabeth; Hruban Ralph H; **Goggins Michael**
CORPORATE SOURCE: Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland, MD 21205-2196, USA.
CONTRACT NUMBER: CA62924 (NCI)
SOURCE: Oncogene, (2002 Mar 27) 21 (13) 2114-7.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020418
Last Updated on STN: 20020511
Entered Medline: 20020510

AB A higher prevalence of epigenetic inactivation of tumor suppressor genes has been reported in cancer cell line populations compared to primary cancer populations. Cancer-related genes are commonly **methylated** in cancer cell lines but it is not known the extent to which tumor suppressor genes may be artificially **methylated** in vitro. We therefore examined 10 **pancreatic cancer** cell lines and corresponding primary tumors for aberrant DNA **methylation** of promoter CpG islands of eight genes and seven CpG islands. Using **methylation**-specific PCR (MSP), **methylation** was not detected at any of the 15 CpG islands in 15 normal pancreata or in an immortalized normal pancreatic duct epithelial (HPDE) cell line. Of 150 loci examined, 49 loci were **methylated** in both primary carcinomas and their corresponding cell lines, 95 loci were not **methylated** in either cell lines or their corresponding primary carcinomas. There were four loci **methylated** only in cell lines while another two loci were **methylated** only in primary carcinomas. Overall, the **methylation** status of primary carcinomas and their cell lines were concordant in 96% of cases (144 of 150) (J statistic; J=0.92, P<0.0001). We conclude that most of the DNA **methylation** of tumor suppressor genes observed in cancer cell lines is present in the primary carcinomas from which they were derived.

L11 ANSWER 14 OF 24 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2002:270109 SCISEARCH
THE GENUINE ARTICLE: 533ZM
TITLE: Identification of hepatocarcinoma-intestine-pancreas/pancreatitis-associated protein I as a biomarker for pancreatic ductal adenocarcinoma by protein biochip technology
AUTHOR: Rosty C; Christa L; Kuzdzal S; Baldwin W M; Zahurak M L; Carnot F; Chan D W; Canto M; Lillemoe K D; Cameron J L; Yeo C J; Hruban R H; **Goggins M (Reprint)**

CORPORATE SOURCE: Johns Hopkins Med Inst, Dept Pathol, 632 Ross Bldg, 720 Rutland Ave, Baltimore, MD 21205 USA (Reprint); Johns Hopkins Med Inst, Dept Pathol, Baltimore, MD 21205 USA; Johns Hopkins Med Inst, Dept Oncol, Baltimore, MD 21205 USA; Johns Hopkins Med Inst, Dept Surg, Baltimore, MD 21205 USA; Johns Hopkins Med Inst, Dept Med, Baltimore, MD 21205 USA; CHU Necker, INSERM, U370, F-75015 Paris, France; CHU Necker, Liver Unit, F-75015 Paris, France; Hop Europeen Georges Pompidou, Serv Anat & Cytol Pathol, F-75015 Paris, France
COUNTRY OF AUTHOR: USA; France
SOURCE: CANCER RESEARCH, (15 MAR 2002) Vol. 62, No. 6, pp. 1868-1875.
Publisher: AMER ASSOC CANCER RESEARCH, PO BOX 11806, BIRMINGHAM, AL 35202 USA.
ISSN: 0008-5472.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 33

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB New biomarkers of pancreatic adenocarcinoma are needed to improve the early detection of this deadly disease. We performed surface enhanced laser desorption ionization (SELDI) mass spectrometry using ProteinChip technology (Ciphergen Biosystems, Fremont, CA) to screen for differentially expressed proteins in pancreatic juice. Pancreatic juice samples obtained from patients undergoing pancreatectomy for pancreatic adenocarcinoma were compared with juice samples from patients with other pancreatic diseases. We identified a peak similar to16,570 daltons present in the pancreatic juice from 10/15 (67%) of the patients with pancreatic adenocarcinoma and in the pancreatic juice from 1/7 (17%) of the patients with other pancreatic diseases. Using a ProteinChip immunoassay, we identified this differentially expressed protein as hepatocarcinoma-intestine-pancreas/pancreatitis-associated-protein I (HIP/PAP-I), a protein released from pancreatic acini during acute pancreatitis and overexpressed in hepatocellular carcinoma. We then quantified by ELISA the pancreatic juice HIP/PAP-I levels in 43 patients (28 with pancreatic adenocarcinoma, 15 with other pancreatic diseases) and the serum HIP/PAP-I levels in 98 patients (53 with pancreatic adenocarcinoma, 45 with other pancreatic diseases or healthy individuals). HIP/PAP-I levels were significantly higher in both the pancreatic juice ($P < 0.001$) and in the serum ($P < 0.001$) of patients with pancreatic adenocarcinoma compared with the control group. HIP/PAP-I levels were similar to1000-fold higher in pancreatic juice compared with serum and the magnitude of the difference between the pancreatic adenocarcinoma group and the control group was greater in the pancreatic juice samples (143.75 +/- 235.52 mug/ml versus 6.04 +/- 7.59 mug/ml) than in the serum samples (99.96 +/- 140.66 ng/ml versus 35.25 +/- 28.44 ng/ml). In our study, patients with pancreatic juice HIP/PAP-I levels greater than or equal to20 mug/ml were 21.9 times (95% confidence interval, 3.5-136.5; $P < 0.001$) more likely to have pancreatic adenocarcinoma than patients with levels <20 mug/ml. Immunolabeling of tissue sections revealed that the HIP/PAP-I protein was strongly expressed in acini adjacent to the invasive adenocarcinoma, but it was only rarely (1/30; 3%) expressed in the neoplastic epithelium, which suggests that the main source of HIP/PAP-I release in the pancreatic juice is acini. This low level of HIP/PAP-I expression in pancreatic adenocarcinoma was confirmed by reverse transcription-PCR: only 1 (5%) of 19 **pancreatic cancer** cell lines expressed HIP/PAP-I transcripts. Taken together, these data suggest that pancreatic juice measurement of HIP/PAP-I may help to identify patients with pancreatic adenocarcinoma.

L11 ANSWER 15 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2002670942 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12432281

TITLE: Aberrant **methylation** of the 5' CpG island of TSLC1 is common in pancreatic ductal adenocarcinoma and is first manifest in high-grade PanlNs.
COMMENT: Comment in: Cancer Biol Ther. 2002 May-Jun;1(3):297-9. PubMed ID: 12432282
AUTHOR: Jansen Marnix; Fukushima Noriyoshi; Rosty Christophe; Walter Kim; Altink Renee; Heek Tjarda Van; Hruban Ralph; Offerhaus Johan G; **Goggins Michael**
CORPORATE SOURCE: Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland 21205, USA.
CONTRACT NUMBER: CA62924 (NCI)
SOURCE: Cancer biology & therapy, (2002 May-Jun) 1 (3) 293-6. Journal code: 101137842. ISSN: 1538-4047.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 20021115
Last Updated on STN: 20031028
Entered Medline: 20031027

AB The recently identified tumor-suppressor gene TSLC1 on chromosome 11q23.2 is frequently inactivated in human non-small cell lung adenocarcinoma by DNA **methylation**-associated silencing. The aim of this study was to determine if TSLC1 is inactivated in adenocarcinoma of the pancreas. We analyzed 17 **pancreatic cancer** cell lines, 91 primary pancreatic adenocarcinoma, 46 pancreatic intraepithelial (PanIN) precursor lesions and 15 microscopically normal pancreata for **methylation** of the 5' CpG island of the TSLC1 gene through **methylation**-specific PCR. We observed 5' CpG **methylation** of TSLC1 in 4 of 17 cell lines (24%). In each cell line the aberrant **methylation** was associated with loss of TSLC1 expression by RT-PCR that was reversible after treatment with the DNA methyl-transferase inhibitor 5-aza-2'- deoxycytidine. Furthermore, we observed that TSLC1 was **methylated** in 25 of 91 primary pancreatic adenocarcinomas (27%), and in 2 of 7 highgrade PanIN-3 lesions (29%), but not in low-grade PanIN (0 of 9 PanlN-2 and 0 of 30 PanIN-1) lesions or in normal pancreata (n=15). We conclude that epigenetic silencing of TSLC1 expression through 5' CpG island associated **methylation** is common in pancreatic adenocarcinoma and is a late event in pancreatic neoplastic development.

L11 ANSWER 16 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2002060515 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11786397
TITLE: Overexpression of S100A4 in pancreatic ductal adenocarcinomas is associated with poor differentiation and DNA hypomethylation.
COMMENT: Comment in: Am J Pathol. 2002 Jan;160(1):7-13. PubMed ID: 11786392
AUTHOR: Rosty Christophe; Ueki Takashi; Argani Pedram; Jansen Marnix; Yeo Charles J; Cameron John L; Hruban Ralph H; **Goggins Michael**
CORPORATE SOURCE: Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland 21205-2196, USA.
CONTRACT NUMBER: P50-CA62924 (NCI)
SOURCE: American journal of pathology, (2002 Jan) 160 (1) 45-50. Journal code: 0370502. ISSN: 0002-9440.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200207
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020707

Entered Medline: 20020705

AB Using the National Center for Biotechnology Information Serial Analysis of Gene Expression database, we found that S100A4, a calcium-binding protein previously implicated in metastasis, was expressed in five of seven pancreatic carcinoma libraries but not in the two normal pancreatic duct libraries. We confirmed the overexpression of S100A4 using reverse transcriptase-polymerase chain reaction, which demonstrated that 18 of 19 (95%) pancreatic carcinoma cell lines expressed S100A4. Using immunohistochemistry, we found that 57 of 61 invasive pancreatic carcinomas (93%), 3 of 18 high-grade pancreatic intraepithelial neoplasia lesions (17%), and 0 of the 69 low-grade pancreatic intraepithelial neoplasia lesions expressed S100A4 protein, whereas normal pancreatic tissue and tissue affected by chronic pancreatitis did not label. Expression of S100A4 was associated with poor differentiation of the pancreatic adenocarcinomas (P = 0.001). We found that three CpG sites in the first intron of the S100A4 gene were approximately 90% **methylated** in microdissected normal pancreatic duct cells using bisulfite-modified sequencing and in two cell lines and three primary pancreatic carcinomas with a reduced or absent expression of S100A4. In contrast, these CpGs were 100% hypomethylated in 11 of 12 **pancreatic cancer** cell lines by **methylation** -specific polymerase chain reaction. The association between the expression of S100A4 and hypomethylation of the first intron of S100A4 was statistically significant (P = 0.002). These data suggest that the majority of pancreatic carcinomas undergo selection for hypomethylation and overexpression of S100A4. Because most pancreatic carcinomas express S100A4, it may be a useful target for early detection strategies.

L11 ANSWER 17 OF 24 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2002:476490 SCISEARCH
THE GENUINE ARTICLE: 558WV
TITLE: Early detection of pancreatic carcinoma
AUTHOR: Rosty C; **Goggins M (Reprint)**
CORPORATE SOURCE: Johns Hopkins Med Inst, Dept Pathol, 720 Rutland Ave, Baltimore, MD 21205 USA (Reprint); Johns Hopkins Med Inst, Dept Pathol, Baltimore, MD 21205 USA; Johns Hopkins Med Inst, Dept Med, Baltimore, MD 21205 USA; Johns Hopkins Med Inst, Dept Oncol, Baltimore, MD 21205 USA
COUNTRY OF AUTHOR: USA
SOURCE: HEMATOLOGY-ONCOLOGY CLINICS OF NORTH AMERICA, (FEB 2002) Vol. 16, No. 1, pp. 37-+.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA.
ISSN: 0889-8588.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 110

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB To improve the dismal prognosis of patients with pancreatic adenocarcinoma, the disease needs to be diagnosed at an earlier and hopefully more curable stage. Individuals at high risk for developing **pancreatic cancer**, such as those with a history of familial **pancreatic cancer**, would greatly benefit from efficient early detection programs. Currently, screening methods consist of imaging techniques and serum CA19-9 levels, which are not optimal for the detection of small pancreatic lesions. The understanding of genetic alterations, in combination with the development of high-throughput sensitive techniques, such as gene expression profiling and proteomics, will hopefully lead to the rapid discovery of a panel of biomarkers that will save lives by enabling aggressive therapy at the time when tumors are curable.

L11 ANSWER 18 OF 24 MEDLINE on STN
ACCESSION NUMBER: 2001689479 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11731440
TITLE: Identification and characterization of **differentially methylated** CpG islands in pancreatic carcinoma.
AUTHOR: **Ueki T**; Toyota M; Skinner H; Walter K M; Yeo C J; Issa J P; Hruban R H; **Goggins M**
CORPORATE SOURCE: Department of Pathology, Johns Hopkins School of Medicine and the Johns Hopkins School of Public Health, Baltimore, Maryland 21205, USA.
CONTRACT NUMBER: 5P50CA62924-07 (NCI)
SOURCE: Cancer research, (2001 Dec 1) 61 (23) 8540-6. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011212
Last Updated on STN: 20020125
Entered Medline: 20020103

AB To identify CpG islands **differentially methylated** in pancreatic adenocarcinoma, we used **methylated** CpG island amplification (MCA) coupled with representational difference analysis. Of 42 CpG islands identified by MCA/representational difference analysis, 7 CpG islands [**methylated** in carcinoma of the pancreas (MICP)] were **differentially methylated** in a panel of eight **pancreatic cancer** cell lines compared with normal pancreas. In a larger panel of 75 pancreatic adenocarcinomas, these 7 MICPs (ppENK, Cyclin G, ZBP, MICP25, 27, 36, and 38) were **methylated** in 93, 3, 9, 15, 48, 19, and 41% of cancers, respectively, by **methylation**-specific PCR but not in any of 15 normal pancreata. In **pancreatic cancer** cell lines, **methylation** of ppENK, a gene with known growth suppressive properties, was associated with transcriptional silencing that was reversible with 5-aza-2'-deoxycytidine treatment. Relationships between the **methylation** patterns of pancreatic adenocarcinomas and their clinicopathological features were also determined. Larger pancreatic cancers and those from older patients (P = 0.017) harbored more **methylated** loci than smaller tumors and those from younger patients (P = 0.017). ppENK, MICP25, and 27 were variably **methylated** in normal gastric, duodenal, and colonic mucosae. These data indicate that aberrant **methylation** of ppENK and its transcriptional repression is a common event in pancreatic carcinogenesis.

L11 ANSWER 19 OF 24 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:492440 BIOSIS
DOCUMENT NUMBER: PREV200200492440
TITLE: Molecular pathology of **pancreatic cancer**
.
AUTHOR(S): Hruban, Ralph H. [Reprint author]; Iacobuzio-Donahue, Christine; Wilentz, Robb E.; **Goggins, Michael**; Kern, Scott E.
CORPORATE SOURCE: Johns Hopkins Hospital, 401 North Broadway, Weinberg 2242, Baltimore, MD, 21231, USA
SOURCE: Cancer Journal, (July-August, 2001) Vol. 7, No. 4, pp. 251-258. print.
ISSN: 1528-9117.
DOCUMENT TYPE: Article
General Review; (Literature Review)
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Sep 2002
Last Updated on STN: 18 Sep 2002

AB Until recently, **pancreatic cancer** was a poorly understood disease. Research in the past decade has shown conclusively,

however, that **pancreatic cancer** is primarily genetic in nature. Inactivation with a variety of tumor-suppressor genes such as p16, DPC4, and p53, coupled with activation of oncogenes such as K-ras, are a few of the mutations that trigger the growth of cancerous cells. Understanding these mutations is critical to a better understanding of familial **pancreatic cancer** and to the development of gene-based screening tests and therapies. In this article, we review the genetic alterations identified in **pancreatic cancer** and provide examples of how this information can be applied to patient care.

L11 ANSWER 20 OF 24 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2000:529624 SCISEARCH
THE GENUINE ARTICLE: 309RU
TITLE: High concordance between DNA **methylation** of tumor suppressor loci in **pancreatic cancer** cell lines and their corresponding primary carcinoma.
AUTHOR: **Ueki T (Reprint)**; Toyota M; Walter K M; Jaffee E; Yeo C J; Hruban R H; **Goggins M**
CORPORATE SOURCE: JOHNS HOPKINS MED INST, BALTIMORE, MD 21205
COUNTRY OF AUTHOR: USA
SOURCE: GASTROENTEROLOGY, (APR 2000) Vol. 118, No. 4, Part 1, Supp. [2], pp. 448-448.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0016-5085.
DOCUMENT TYPE: Conference; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 0

L11 ANSWER 21 OF 24 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2000305473 EMBASE
TITLE: Can we screen high-risk individuals to detect early pancreatic carcinoma?.
AUTHOR: **Goggins M.**; Canto M.; Hruban R.
CORPORATE SOURCE: Dr. M. Goggins, Department of Pathology, 632 Ross Building, Johns Hopkins Medical Institutions, 720 Rutland Ave, Baltimore, MD 21205-2196, United States. mgoggins@jhmi.edu
SOURCE: Journal of Surgical Oncology, (2000) 74/4 (243-248).
Refs: 52
ISSN: 0022-4790 CODEN: JSONAU
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 009 Surgery
016 Cancer
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB An estimated 10% of individuals with **pancreatic cancer** have an inherited predisposition to the disease. Germline mutations in BRCA2, p16, STK11, and the cationic trypsinogen gene contribute to inherited forms of **pancreatic cancer**, but the gene(s) responsible for much of the familial **pancreatic cancer** burden remains to be identified. The high lifetime risk of **pancreatic cancer** that exists among at-risk members of families with multiple pancreatic cancers highlights the pressing need for **pancreatic cancer** early detection strategies. Since curative pancreatic resection is still the only curative treatment for most patients with **pancreatic cancer**, the early detection of symptomless **pancreatic cancer** using endoscopic ultrasound or molecular markers may provide the best chance of

cure for individuals at high risk of this disease. (C) 2000 Wiley-Liss, Inc.

L11 ANSWER 22 OF 24 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:254520 BIOSIS
DOCUMENT NUMBER: PREV200000254520
TITLE: High concordance between DNA **methylation** of tumor suppressor loci in **pancreatic cancer** cell lines and their corresponding primary carcinoma.
AUTHOR(S): Ueki, Takashi [Reprint author]; Toyota, Minoru [Reprint author]; Walter, Kimberly M. [Reprint author]; Jaffee, Elizabeth [Reprint author]; Yeo, Charles J. [Reprint author]; Hruban, Ralph H. [Reprint author]; **Goggins, Michael** [Reprint author]
CORPORATE SOURCE: The Johns Hopkins Med Institutions, Baltimore, MD, USA
SOURCE: Gastroenterology, (April, 2000) Vol. 118, No. 4 Suppl. 2 Part 1, pp. A46. print.
Meeting Info.: 101st Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Diego, California, USA. May 21-24, 2000. American Gastroenterological Association.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Jun 2000
Last Updated on STN: 5 Jan 2002

L11 ANSWER 23 OF 24 MEDLINE on STN
ACCESSION NUMBER: 1999365827 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10436774
TITLE: Progress in cancer genetics: lessons from **pancreatic cancer.**
AUTHOR: **Goggins M**; Kern S E; Offerhaus J A; Hruban R H
CORPORATE SOURCE: Department of Oncology, Johns Hopkins Medical Institutions, Baltimore, MD, USA.
CONTRACT NUMBER: P50-CA62824 (NCI)
SOURCE: Annals of oncology : official journal of the European Society for Medical Oncology / ESMO, (1999) 10 Suppl 4 4-8. Ref: 87
Journal code: 9007735. ISSN: 0923-7534.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 19990921
Last Updated on STN: 19990921
Entered Medline: 19990909

AB BACKGROUND: In the near future advances in the molecular basis of cancer are expected to facilitate cancer diagnosis, to rationalize treatment, to facilitate screening, and to identify individuals requiring cancer prevention strategies. METHODS: The literature was reviewed concerning the genetic alterations that contribute to **pancreatic cancer** development. RESULTS: Virtually all pancreatic cancers have inactivation of the p16 pathway, and the majority inactivate the TGF beta/DPC4 and p53 tumor-suppressive pathways. Pancreatic cancers with mismatch repair deficiency have a characteristic histology and may have an improved prognosis. The recently discovered tumor suppressor genes, ALK-5, MKK4, and STK11 (the gene responsible for Peutz-Jeghers syndrome) are all targeted for mutation in a small proportion of sporadic pancreatic cancers. Germline mutations of the BRCA2 gene are present in 5-10% of

patients with **pancreatic cancer**. Typically such patients do not have a family history of **pancreatic cancer** and are mistaken as patients with sporadic disease. Five to 10% of patients with **pancreatic cancer** have first-degree relatives that will develop **pancreatic cancer**. Some such families also have a family history of melanoma and harbor germline p16 mutations. However, the gene(s) responsible for much of the inherited predisposition to **pancreatic cancer** remain to be identified. CONCLUSION: Further advances in **pancreatic cancer** molecular genetics are needed to facilitate the development of molecular screening tests, to identify additional familial susceptibility genes, and to identify targets for rational therapeutic targeting.

L11 ANSWER 24 OF 24 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1998:112879 SCISEARCH
THE GENUINE ARTICLE: YU374
TITLE: Analysis of PTEN/MMAC1 alterations in aerodigestive tract tumors
AUTHOR: Okami K; Wu L; Riggins G; Cairns P; **Goggins M**; Evron E; Halachmi N; Ahrendt S A; Reed A L; Hilgers W; Kern S E; Koch W M; Sidransky D; Jen J (Reprint)
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ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB PTEN/MMAC1 is a candidate tumor suppressor gene recently identified at chromosomal hand 10q23. It is mutated in sporadic brain, breast, and prostate cancer and in the germ line of patients with hereditary Cowden disease. We searched for genetic alterations of the PTEN/MMAC1 gene in 39 primary head and neck cancers (HNSCCs), 42 primary non-small cell lung cancers (NSCLCs), 80 **pancreatic cancer** xenografts, and 37 cell lines and xenografts from colon, lung, and gastric cancers. Microsatellite analysis revealed loss of heterozygosity at markers near the gene in 41% of primary HNSCCs, 50% of NSCLCs, and 39% of the pancreatic cancers. Three cases of HNSCCs displayed homozygous deletion involving the gene. We sequenced the entire coding region of the PTEN/MMAC1 gene in the remaining tumors displaying loss of heterozygosity and found one terminating mutation in a HNSCC sample. Thus, a second inactivation event was observed in 4 of 39 primary HNSCC cases. By use of a protein truncation assay, one terminating mutation was also identified in one of eight NSCLC cell lines. Our results suggest that PTEN/MMAC1 gene inactivation plays a role in the genesis of some tumor types.

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FILE 'HOME' ENTERED AT 15:17:44 ON 21 APR 2004

FILE 'MEDLINE, BIOTECHDS, EMBASE, BIOSIS, SCISEARCH, CANCERLIT, CAPLUS'
ENTERED AT 15:20:43 ON 21 APR 2004

L1	1509	S GOGGINS M?/AU OR UEKI T/AU
L2	7576	S PREPROENKEPHALIN OR PPENK OR MET5-ENKEPHALIN
L3	456587	S METHYLA? OR HYPERMETHYLATION OR DIFFERENTIALLY METHYLA?
L4	227492	S PANCREATIC CANCER OR COLORECTAL CANCER OR COLON CANCER
L5	3628	S L4 AND L3
L6	17	S L5 AND L2
L7	10	DUP REM L6 (7 DUPLICATES REMOVED)
L8	123	S L1 AND L3
L9	44	DUP REM L8 (79 DUPLICATES REMOVED)
L10	24	S L9 AND L4
L11	24	DUP REM L10 (0 DUPLICATES REMOVED)